U.S. High Production Volume (HPV)
Chemical Challenge Program

201-16142A

SUMMARY OF EXISTING DATA, PROPOSED TEST PLAN AND RATIONALE FOR HEXANOIC ACID, 2-ETHYL, ZIRCONIUM SALT (CASRN 22464-99-9)

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DATE: AUGUST 11, 2005

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INTRODUCTION

The following document includes a test plan and a summary of existing data for hexanoic acid, 2-ethyl, zirconium salt [CASRN 22464-99-9]. The information provided in this document and the attached dossier of robust summaries meets the requirements under the U.S. High Production Volume (HPV) Chemical Challenge. Hexanoic acid, 2-ethyl, zirconium salt is one of 19 sponsored chemicals organized under the Metal Carboxylates Coalition (The Coalition), an HPV testing consortium managed by the Synthetic Organic Chemical Manufacturers Association's (SOCMA) VISIONS Department. The Coalition member companies sponsoring hexanoic acid, 2-ethyl, zirconium salt are OM Group, Inc., The Shepherd Chemical Company and Troy Corporation.

USE PATTERNS AND REGULATORY BACKGROUND

Hexanoic acid, 2-ethyl, zirconium salt is also known as zirconium hexanoate or zirconium octanoate. This compound is the zirconium salt of hexanoic acid, which is a C-8 carboxylic acid ($C_8H_{16}O_2$), and a member of the metal carboxylates group. The structure of hexanoic acid, 2-ethyl, zirconium salt is presented in Figure 1.

Figure 1: Structure of hexanoic acid, 2-ethyl, zirconium salt

All of the metal carboxylate salts are designed to add metals to chemical reactions. They therefore are expected to dissociate into free metal and free acid.

Hexanoic acid, 2-ethyl, zirconium salt is used in products as a paint drier. It is often used in combination with cobalt, manganese, and/or calcium in various combinations to provide the desired drying properties (i.e., different paints require different drying properties depending upon their applications).

One characteristic of hexanoic acid, 2-ethyl, zirconium salt and other metal carboxylates is that they readily dissociate from an ion pair into free metal and free acid. They are found as partially dissociated products in the ambient environment (i.e., neutral pH). Dissociation is a reversible process and the proportion of dissociated salt is dependent on the pH and pKa (the dissociation constant), which is the pH at which 50% dissociation occurs. In the low pH environment of the digestive tract (e.g., pH 1.2) complete dissociation will occur for these metal carboxylates. The transport and bioavailability of the metals and acids are determined by their solubility in environmental media and biological fluids which is determined by environmental parameters such as pH.

Dissociation is a reversible reaction, splitting the parent compound into two or more chemical species which may be ionic, but are not necessarily so. The process can be generally represented as:

$$[RCOO^-]_x{:}[M^+] \overset{pK1}{\leftrightarrow} [RCOO^-]_x + [M^+] \overset{pK2}{\leftrightarrow} [RCOOH]_x + [M^+]$$

undissociated salt — **dissociated acid and metal** — **neutral species + ionized metal**

High pH — Low pH

The pKa and pH are equal when the metal carboxylate salt is 50% dissociated. The parent compounds, the metal carboxylate salts, are associated ionized molecules.

The Metal Carboxylates Coalition conducted a study following OECD Guideline 112 to determine the dissociation constant of hexanoic acid, 2-ethyl, zirconium salt. The mean pKa values were 5.81, 7.09, 7.65, and 8.24 at 20ºC. These results indicate that about 50% dissociation will occur at approximately neutral pH (i.e., representative of aquatic and marine ecosystems), while complete dissociation will occur at the physiologically relevant pH of the mammalian stomach (pH 1.2). These findings are particularly important in relating available data for 2-ethylhexanoic acid and zirconium to support the existing data for hexanoic acid, 2-ethyl, zirconium salt in the fulfillment of critical endpoints.

Because the free acid (2-ethylhexanoic acid) and corresponding free metal (zirconium) have different characteristics (e.g., solubility, adsorption, and toxicity) than the undissociated salt (ion pair), the proportion of dissociation influences the behavior of the substance in the environment and *in vivo*. The bioavailable

fraction of the constituents of metal carboxylate salts can be estimated from the dissociation constants.

There are two principal hazard assessments being evaluated based on the current data for hexanoic acid, 2-ethyl, zirconium salt. The first is the hazard to aquatic organisms due to environmental exposure. The second is hazard to mammalian systems as a result of oral exposure. Based upon the pKa of 5.81 to 8.24, it is expected that in the ambient aquatic environment, moderate portions of the hexanoic acid, 2-ethyl, zirconium salt will be dissociated; therefore, part of the compound will be present as 2-ethylhexanoic acid and zirconium cations. In the environment (i.e., aquatic systems), toxicity is typically related to the free metal ion concentration (U.S. EPA, 2002). The metal ion pair (salt) is less likely to be absorbed and to contribute to toxicity. Toxicity data for a simple salt of zirconium (zirconium tetrachloride) are used to estimate the potential hazard of the zirconium component of hexanoic acid, 2-ethyl, zirconium salt to aquatic organisms. Data for zirconium oxychloride ($ZrOCl_2$) are also relevant, since this compound is formed rapidly from zirconium tetrachloride ($ZrCl_4$) in water.

At the low pH of the mammalian stomach (pH 1.2) all of the metal carboxylates, including hexanoic acid, 2-ethyl, zirconium salt, are expected to be completely, or nearly completely, dissociated. This indicates that when administered orally, the absorption and resulting toxicity would be due to the independent action of the 2-ethylhexanoic acid and the free (ionized) zirconium. Although there are no data available specifically for zirconium-containing carboxylates, this scenario is supported by *in vitro* data with cobalt acetate and other cobalt containing carboxylates (Firriolo 1992.; Speijers et al 1985; Stopford et al. 2003) (See discussion below).

The dissociation constant shows that at the pH of the stomach, the important moieties from a toxicological standpoint are the unionized free 2-ethylhexanoic acid and ionized zirconium. Because of this dissociation in the stomach, mammalian toxicity data for 2-ethylhexanoic acid can to serve as a surrogate data for the carboxylic acid component of hexanoic acid, 2-ethyl, zirconium salt. Similarly, under these conditions, data for zirconium can be represented by fate and toxicity data for free ion or simple metal salts (e.g., zirconium tetrachloride and zirconium oxychloride). Therefore, the role in any observed toxicity for acids and metals can be evaluated independently.

Bioequivalency

The work described below by Stopford et al. (2003) shows that cobalt chloride is similar to, or more bioavailable than, the corresponding cobalt carboxylate salts, which makes the chloride a conservative surrogate in estimating bioavailability and toxicity of dissociated metal. This is analogous to the situation with other metal carboxylates; therefore, zirconium tetrachloride has been emphasized

during preparation of the attached robust summaries and provides the preferred surrogate data for hexanoic acid, 2-ethyl, zirconium salt.

The recent studies by Stopford et al. to evaluate the "bioequivalency" (an estimate of bioavailability) of cobalt compounds included three cobalt carboxylates and cobalt chloride (when added as fine powders) in synthetic fluids designed as surrogate gastric juices. These investigators showed that these cobalt salts were completely dissociated and dissolved at a gastric pH (1.2) (Table 1). When added to surrogate intestinal fluids at neutral pH (7.4), $Co(II)Cl_2$ was also highly soluble. The solubility of the cobalt (% available cobalt expressed as Co(II) ion) in cobalt carboxylates ranged from 30.8 to 50.8 percent available cobalt at 72 hours (Table 1). These results for cobalt chloride and cobalt naphthenate are highly consistent with data reported by Firriolo (1992) for these same salts in similar surrogate biological fluid matrix (Table 1). Maximum solubility of cobalt naphthenate was observed at 48 hrs, which was the longest sample time used in the study.

These bioequivalency data are valuable for two reasons. They confirm the prediction from the dissociation studies that metal carboxylates, including those containing Co and Zr, are expected to be completely dissociated in the gastrointestinal tract (low pH) and a substantial proportion of these compounds would be expected to be dissociated and bioavailable in water at neutral pH (7.4).

Table 1: Results of extraction of cobalt from surrogate biological fluids

Matrix (pH)	**Maximum Solubility (% of available metal)**			
	$CoCl_2$	Co 2-ethyl-hexanoate	Co naphthenate	Co neodecanoate
Gastric pH (1.5)[a]	100	100	100	100
Gastric pH (2.0)[b]	100		100	--
Intestinal pH (7.4)[a]	100	50.8*	45.4*	30.8*
Intestinal pH (7.3)[b]	85	--	20**	--

[a] From Stopford et al. (2003); [b] Firriolo (1992)

* Maximum concentration observed at 72 hours.

** Maximum concentration observed at 48 hours.

Stopford et al. (2003) and Firriolo (1992) added all of the salts to the neutral (intestinal) surrogate solutions as finely ground powder. It is not surprising that the percent of available cobalt from cobalt carboxylates appears to increase with time (48 or 72 hours). Firriolo (1992) also evaluated the solubility of ground and ethanol-solubilized cobalt naphthenate in a neutral buffer solution[1]. For ground cobalt naphthenate, 20% of available Co(II) was dissociated. In contrast, 90% of available cobalt was observed as dissociated Co(II) when originally introduced in

[1] PBS = phosphate buffered solution without $CaCl_2$ or $MgCl_2$

ethanol. The ethanol-solubilized Co(II) remained in solution. This finding has implications for dissociated Co(II) introduced to the intestine solubilized in gastric juices.

Cobalt is absorbed primarily as the free Co(II) ion via biochemical mechanisms at the intestinal mucosal wall (Firriolo 1992). Having been reported as completely soluble in gastric fluids (Stopford et al. 2003; Firriolo 1992), Co(II) should remain soluble (100% dissociated Co(II)) after entering the intestine from the stomach. Once solubilized, this cobalt would be expected to undergo the same fate as any other source of Co irrespective of the salt originally ingested. Other metals, including zirconium, are expected to behave similarly. Although the rate of absorption, distribution and elimination of Zr is different from Co, in each case the metal moiety will enter the small intestine independent of the carboxylic acid or other ion. The absorption and toxicity of Zr are discussed below.

Finally, the work by Stopford et al. (2003) shows that the metal chloride is similar to, or more bioavailable than, the corresponding metal carboxylate salts (Table 1), which makes the chloride a conservative surrogate when attempting to estimate the bioavailability and toxicity of dissociated metal salts. For this reason, data for the chlorides of zirconium have been emphasized during preparation of the attached robust summaries and is the preferred surrogate for the zirconium dissociation product of hexanoic acid, 2-ethyl, zirconium salt.

Supporting Data for Dissociation Products

Consistent with discussions between the Metal Carboxylates Coalition and the EPA, data for the dissociation products (metals and acids) are recognized as being essential to understanding the environmental fate and toxicological characteristics of the respective metal carboxylate salts. Data for 2-ethylhexanoic acid and chlorides of zirconium (primarily zirconium tetrachloride, and to a lesser degree, zirconium oxychloride) are therefore useful in characterizing the hazard of hexanoic acid, 2-ethyl, zirconium salt.

In summary, the key points relative to hexanoic acid, 2-ethyl, zirconium salt are:

- Dissociation to 2-ethylhexanoic acid and zirconium (described as zirconium tetrachloride or zirconium oxychloride);
- Dissociation constant (pK values) in the circum neutral range;
- Complete or nearly complete dissociation at gastric pH (1.2);
- A moderate amount of dissociation in the environmental pH range (neutral);
- Existing data for the parent molecule or its dissociation products will be sufficient to address specific endpoints.

Data for hexanoic acid, 2-ethyl, zirconium salt and its dissociation products are provided as follows:

1. Data for hexanoic acid, 2-ethyl, zirconium salt [CASRN 22464-99-9] are provided in robust summary format in Appendix A.

2. In addition, when available, data for the dissociation products (2-ethylhexanoic acid and zirconium tetrachloride/oxychloride) are provided.

    a. Appendix B contains robust summaries for 2-ethylhexanoic acid [CASRN 149-57-5].
    b. Appendix C contains robust summaries for zirconium tetrachloride [CASRN 10026-11-6]. Where available, data for zirconium oxychloride [CASRN 7699-43-6] are also included. (In aqueous solutions, zirconium oxychloride is rapidly formed from zirconium tetrachloride).

2-ethylhexanoic acid

2-ethylhexanoic acid is used in the manufacture of lubricants, detergents, floatation aids, and corrosion inhibitors, as catalysts for solvent extraction, and for dye granulation, and in the production of alkyd resins used for baking enamels (HSDB, 2005).

For both oral and intravenous administration of 2-ethylhexanoic acid, most (64 – 75%) of the dose was excreted in the urine, with fecal excretion ranging from 2 – 12%. After oral administration, peak blood levels were achieved after 15 to 30 minutes. Dermally-applied compound was both absorbed more slowly and excreted more slowly.

The robust summaries for 2-ethylhexanoic acid were made available to the Coalition by the American Chemistry Council Oxo Process Panel, the members of which volunteered to provide the information to the OECD SIDS program. These robust summaries are attached as Appendix B. In addition, these data are summarized and referenced in the appropriate remarks sections for each data element in the robust summaries for hexanoic acid, 2-ethyl, zirconium salt (Appendix A). Data for 2-ethylhexanoic acid are discussed in the next section and summarized in Table 2.

Zirconium

Zirconium is a naturally-occurring element that is found (only in combined states) in the earth's crust, in amounts larger than lead, copper or zinc. It is taken up by plants from soil and water and accumulated in certain tissues. It is found in all animal tissues, with retention initially in soft tissues and then slowly in the bone. The level of toxicity has been found to be moderately low, and toxic effects

induced by very high concentrations are nonspecific in nature. Zirconium is apparently neither an essential element nor a toxic element in the conventional sense. The average body burden is 250 mg (HSDB, 2005; Ghosh et al., 1992). The biochemical properties of zirconium include a high affinity for phosphate groups and an inhibitory effect on many enzymes, such as ATPase, pyrophosphatase and blood phosphatases (Couture et al., 1989).

Mineral forms of zirconium are used in a number of alloys, abrasives, lacquers, enamels, paints, tanning agents and waxes. As an insoluble silicate, Zr is used in the cosmetic and deodorant industry. As a tetrachloride, it has been used to precipitate phosphorus in water systems, with the goal of reducing eutrophication potential (Couture et al., 1989).

Studies on the toxicological properties of zirconium have been conducted with various zirconium compounds, the most relevant of which are the simple salts, zirconium tetrachloride and zirconium oxychloride. In this document, data on the toxicity of zirconium as $ZrCl_4$ or $ZrOCl_2$ are used as surrogates for the toxicity of zirconium that is released through the dissociation of hexanoic acid, 2-ethyl, zirconium salt.

Zirconium salts when parenterally administered are slowly absorbed from injection sites, with higher absorption and retention in bone occurring in young rats versus adult or old animals. Orally-ingested zirconium salts are poorly absorbed. Absorbed zirconium is either sequestered in the skeleton or excreted very rapidly. (HSDB, 2005). In studies with rats, the small fraction of orally administered zirconium that was absorbed was selectively fixed in the ovaries, and to a lesser degree in the lung and bone (DeLongeas et al., 1983). Excretion is mainly through the feces (for the non-absorbed zirconium) and through the urine (for the absorbed zirconium).

The robust summaries for zirconium tetrachloride are presented in Appendix C. For some endpoints, available data for zirconium oxychloride are also included. In addition, these data are summarized and referenced in the appropriate remarks sections for each data element in the robust summaries of hexanoic acid, 2-ethyl, zirconium salt (Appendix A). Data for the soluble/dissociable forms of the metal (free metal, or the chloride or oxychloride salt) are discussed in the next section and summarized in Table 2.

EXISTING DATA FOR HEXANOIC ACID, 2-ETHYL, ZIRCONIUM SALT AND DISSOCIATION PRODUCTS - SUMMARY

Physicochemical Properties

Available physicochemical property data for hexanoic acid, 2-ethyl, zirconium salt, and for 2-ethylhexanoic and zirconium tetrachloride, are shown in Table 2 and briefly summarized below. The sources of information for these data are given in the robust summaries (Appendixes A – C).

Recent studies were conducted to determine the boiling point, melting point and water solubility for hexanoic acid, 2-ethyl, zirconium salt. Data for the majority of the relevant physico-chemical endpoints are also available for 2-ethylhexanoic acid and zirconium tetrachloride.

Melting Point

A GLP study was conducted according to OECD Guideline 102 to determine the melting point/melting range of hexanoic acid, 2-ethyl, zirconium salt. The freezing point could not be determined under the conditions of the study and the freezing point is reported as <-75°C. For 2-ethylhexanoic acid, the melting point/freezing point was reported as -118.4°C; and for zirconium tetrachloride, 437ºC.

Boiling Point

A GLP study was conducted according to OECD Guideline 103, using the thermal analysis method, to determine the boiling point/boiling range of hexanoic acid, 2-ethyl, zirconium salt. The boiling range was 204.5 – 206.8ºC. For 2-ethylhexanoic acid, the boiling point was reported as 227.63°C; no data were available for zirconium tetrachloride.

Density

The density for zirconium tetrachloride is reported as 2.803 at 15ºC.

Vapor Pressure

The reported vapor pressure for 2-ethylhexanoic acid was 1.33×10^{-3} kPa at 20ºC. The reported vapor pressure for zirconium tetrachloride was 1 mmHg at 190ºC.

Partition Coefficient

The octanol/water partition coefficient is not applicable for inorganic chemicals such as zirconium tetrachloride. The log octanol/water partition

coefficient was calculated as 3.0 for 2-ethylhexanoic acid and as 4.37 for hexanoic acid, 2-ethyl, zirconium salt.

Water Solubility

A GLP study was conducted, following OECD Guideline 105, using the flask shaking method, to determine the water solubility of hexanoic acid, 2-ethyl, zirconium salt. The water solubility was determined to be 0.5 μg/L at 20ºC. The water solubility of 2-ethylhexyanoic acid was reported to be 25 mg/L at 25ºC. Zirconium tetrachloride is soluble in cold water and very hygroscopic.

Environmental Fate and Transport

Available environmental fate and transport data for hexanoic acid, 2-ethyl, zirconium salt, and for 2-ethylhexanoic acid and zirconium tetrachloride (and other zirconium salts, as available and relevant) are shown in Table 2 and briefly summarized below. The sources of information for these data are given in the robust summaries (Appendixes A – C).

Data exist for dissociation in water for hexanoic acid, 2-ethyl, zirconium salt, but not for any other fate characteristics. Relevant information for the dissociation products is discussed below.

Photolysis

2-ethylhexanoic acid is predicted to undergo indirect photolysis with a half-life of 16 hours, according to AOP v.1.91 in the EPIWIN v.311 program. The photodegradability of zirconium tetrachloride is not relevant, as the element zirconium does not degrade further.

Dissociation in water

One key characteristic of any metal carboxylate is that it readily dissociates from an ion pair into free metal and free acid as the pH is decreased. A dissociation study was conducted according to OECD 112, under GLPs, to determine the equilibrium constant of hexanoic acid, 2-ethyl, zirconium salt. The results indicate pKa values of 5.81, 7.09, 7.65, and 8.24 at 20ºC (Lezotte and Nixon, 2002).

Biodegradation

No data are available on biodegradation of hexanoic acid, 2-ethyl, zirconium salt. In a study with non-acclimated activated sludge, aerobic biodegradation of 2-ethylhexanoic acid was demonstrated, with BOD_5, BOD_{10}, and BOD_{20} at 60%, 76%, and 83%, respectively, of theoretical. Biodegradation is not relevant for the element zirconium.

Monitoring data

No monitoring data were reported.

Transport data

Estimation of environmental transport for hexanoic acid, 2-ethyl, zirconium salt is not available since fate models generally used do not accurately predict salts such as metal carboxylates. However, the distribution of 2-ethylhexanoic acid was predicted using the Level III Fugacity model in EPIWIN v.3.11. Assuming equal input to all compartments, the distribution was predicted as 5.29% in air, 41.6% in water, 53% in soil and 0.197% in sediment, and the persistence time was predicted as 190 hours.

Ecotoxicity

Available ecotoxicity data for hexanoic acid, 2-ethyl, zirconium salt are shown in Table 2 and briefly summarized below. The sources of information for these data are given in the robust summaries (Appendixes A – C).

Fish Toxicity

Hexanoic acid, 2-ethyl, zirconium salt
The available data on the toxicity of hexanoic acid, 2-ethyl, zirconium salt to fish are not reliable due to a number of problems with the two reported studies. However, the dissociation products are reported to be of medium or low toxicity to fish.

2-ethylhexanoic acid
In a static acute test, the reported 96h-LC50 for the fathead minnow (*Pimephales promelas*) was 70 mg/L at a pH of 5.3 – 5.5 in test solutions that were not buffered.

Zirconium tetrachloride
The 96-h LC50 for rainbow trout (*Oncorhynchus mykiss*) was reported to be greater than 20 mg Zr/L, as was the sublethal effects threshold. For coho salmon (*Oncorhynchus kisutch*) fingerlings, the LC50 was greater than 10 mg/L for both 96-hour and 240-hour exposures. LC50 values of 15 – 270 mg Zr/L were reported for zirconium oxychloride for bluegill and fathead minnow.

Invertebrate toxicity

Hexanoic acid, 2-ethyl, zirconium salt
There are no reliable data on the toxicity of hexanoic acid, 2-ethyl, zirconium salt to invertebrate species. Limited data on the dissociation products indicate that they are reported to be of slight or medium toxicity to invertebrates.

2-ethylhexanoic acid
The 48-h EC50 for *Daphnia magna* was reported to be 85.38 mg/L.

Zirconium tetrachloride
A value of 2 mg Zr/L as the 3-week LC50 is reported in the U.S. EPA ECOTOX database for *Daphnia magna*. However, a 3-week LC50 is not a standard endpoint, and the data are from a secondary reference and not considered reliable.

Algal toxicity

Hexanoic acid, 2-ethyl, zirconium salt
The available study on the toxicity of hexanoic acid, 2-ethyl, zirconium salt to algae is not considered reliable. However, data exist for the dissociation products.

2-ethylhexanoic acid
For the green alga *Scenedesmus subspicatus*, the 96-h E_bC50 (EC50 based upon biomass) was reported to be 40.616 mg/L while the 96-h E_rC50 (EC50 based upon growth rate) was reported to be 44.390 mg/L.

Zirconium tetrachloride
For the green alga *Selenastrum capricornutum*, the 96-h EC50 was reported to be 2.6 mg Zr/L.

In summary, there are no reliable ecotoxicity data on hexanoic acid, 2-ethyl, zirconium salt. 2-ethylhexanoic acid is moderately toxic to fish, invertebrates, and algae. Zirconium poses slight to moderate toxicity to fish, but appears to be somewhat more toxic to algae. Reliable data on zirconium toxicity to invertebrates are lacking.

Human Health Effects

Data are available for acute mammalian toxicity and genotoxicity of hexanoic acid, 2-ethyl, zirconium salt, as well as for the dissociation products. All human health effects endpoints are satisfied for 2-ethylhexanoic acid, while most are satisfied for zirconium tetrachloride. These data are shown in Table 2 and briefly summarized below. The sources of information for these data are given in the robust summaries (Appendixes A – C).

Acute Mammalian Toxicity

Hexanoic acid, 2-ethyl, zirconium salt
For hexanoic acid, 2-ethyl, zirconium salt, acute toxicity data are available for five of five acute endpoints (i.e., oral toxicity, inhalation toxicity, dermal

toxicity, skin irritation and eye irritation) as presented in Table 2. A low order of acute toxicity is demonstrated for hexanoic acid, 2-ethyl, zirconium salt. Oral, inhalation and dermal LD50 or LC50 values are >5000 mg/kg (rat), >8.8 mg/L (1 hr., rat), and >5000 mg/kg (rabbit), respectively. Hexanoic acid, 2-ethyl, zirconium salt was not a primary skin irritant or eye irritant to rabbits but was a primary skin irritant and fatiguing agent to guinea pigs.

2-ethylhexanoic acid

Acute toxicity data are available for 2-ethylhexanoic acid for five of five acute endpoints (i.e., oral toxicity, inhalation toxicity, dermal toxicity, skin irritation and eye irritation) as presented in Table 2. The oral LD50 is 1600 - 3200 mg/kg (rat) and the inhalation LC50 is >2.36 mg/L (6 hr, rat). The dermal LD50 for the guinea pig is < 5.0 mL/kg for an undiluted solution of 2-ethylhexanoic acid. For rabbits, 2-ethylhexanoic acid cause slight necrosis in the skin after 4 hours and severe corneal irritation in the eyes after 24 hours.

Zirconium tetrachloride (or other salts)

Zirconium salts have a low oral toxicity due to poor adsorption. The oral LD50 has been determined for both zirconium tetrachloride and zirconium oxychloride, with the former being slightly more toxic. The oral LD50 for zirconium tetrachloride is 438 mg/kg for the mouse and 700 mg/kg for the rat. The oral LD50 for zirconium oxychloride is 1227 mg/kg for the mouse and 3500 mg/kg for the rat. Inhalation of zirconium tetrachloride (6 mg Zr/m^3) for 60 says produced effects in rats, guinea pigs and dogs. The dermal LD50 is unknown. Zirconium compounds are eye irritants but have not caused skin sensitization in guinea pigs or mice. Dermal exposure to zirconium in topical poison ivy medications and deodorants has resulted in granulatomous lesions, probably due to a hypersensitivity reaction.

Repeated Dose Toxicity

Hexanoic acid, 2-ethyl, zirconium salt

There are no repeat dose data available for hexanoic acid, 2-ethyl, zirconium salt.

2-ethylhexanoic acid

Several repeated dose studies have been conducted on 2-ethylhexanoic acid in feed for rats and mice; these studies have yielded consistent results. In the preferred study, rats were fed diets containing three doses of 2-ethylhexanoic acid for 13 weeks, followed by 28 days of recovery. The NOAEL was approximately 300 mg/kg-day and the NOEL was approximately 65 mg/kg-day. The observed changes in hematological parameters and organ weights were reversible within 28 days. No mortality or treatment-related signs of toxicity occurred. In a similar study with mice, the NOAEL was approximately 200 mg/kg-day.

Zirconium tetrachloride (or other salts)
Data are available for zirconium oxychloride and zirconium sulfate. Daily dosing for 16 days of rats via gastric tube with 800 mg/kg zirconium oxychloride (230 mg Zr/kg), which was the only dose level used, did not affect survival, behavior or growth. Histopathology revealed no differences between control and treated animals with the exception of ovarian tissue, which was hypervascularized even after one month post-exposure. In life-time studies with rats in which zirconium sulfate was administered in the drinking water at a level of 5 ppm (with an additional 2.6 ppm in the solid diet), no evidence was found of any biological or toxicological activity of zirconium, except to affect the body weight of older animals in an inconsistent manner.

Genetic Toxicity – in vitro

Hexanoic acid, 2-ethyl, zirconium salt
In the Ames assay, no mutagenic activity was observed in five strains of *Salmonella typhimurium* (e.g., TA98, TA100, TA1535, TA1537 and TA1538), tested with and without metabolic activation. Hexanoic acid, 2-ethyl, zirconium salt was also negative in the bacterial DNA damage/repair assay with *Escherichia coli*, tested with and without metabolic activation.

2-ethylhexanoic acid
2-ethylhexanoic acid yielded negative results in the Ames assay against four strains of *Salmonella typhimurirum* (e.g., TA 97, TA98, TA100, and TA1535) when tested with and without metabolic activation.

Zirconium tetrachloride (or other salts)
Zirconium tetrachloride was negative in the His^+ reverse fluctuation assay with three strains of *Salmonella typhimurium* (e.g., TA97, TA100 and TA102). There were no significant differences in reversions relative to the controls and no dose-related effects on mutations. Zirconium tetrachloride was also negative in the SOS Chromotest, a bacterial DNA damage/repair assay using *E. coli* strain PQ37, with and without metabolic activation. Zirconium oxychloride was also negative in the Ames assay.

Genetic Toxicity – in vivo

Hexanoic acid, 2-ethyl, zirconium salt
No evidence of mutagenic potential was found subsequent to administration of two oral doses of hexanoic acid, 2-ethyl, zirconium salt (using three dose levels) in the mouse micronucleus assay.

2-ethylhexanoic acid
2-ethylhexanol, which metabolizes to 2-ethylhexanoic acid, was negative in the mouse micronucleus assay subsequent to intraperitoneal injection.

Zirconium tetrachloride (or other salts)
Using zirconium oxychloride, mice given a single oral administration at doses of 220 - 225 mg Zr/kg, 734 - 750 mg Zr/kg, and 2220 – 2250 mg Zr/kg demonstrated a dose-dependent increase in chromosomal aberrations in bone marrow cells. Zirconium oxychloride also caused a dose-dependent increase in the incidence of chromosomal aberrations and sister chromatid exchanges in human peripheral blood leucocytes.

In summary, hexanoic acid, 2-ethyl, zirconium salt and 2-ethylhexanoic acid do not appear to be genotoxic. Zirconium tetrachloride and related zirconium salts, although negative in various *in vitro* studies, have shown positive results in *in vivo* studies.

Developmental Studies

Hexanoic acid, 2-ethyl, zirconium salt
No developmental toxicity studies are available for hexanoic acid, 2-ethyl, zirconium salt.

2-ethylhexanoic acid
Several teratogenicity/developmental studies have been conducted with 2-ethylhexanoic acid. The most reliable study was conducted using rats and rabbits, treated by gavage. Rats were dosed on gestation days 6 -15 (0, 100, 250 and 500 mg/kg) and dams euthanatized on day 21. Rabbits were dosed on gestation days 6 -18 (0, 25, 125 and 250 mg/kg) and euthanatized on day 29. No evidence of teratogenicity was found in either species. For rats, the NOEL for offspring was 100 mg/kg-day based upon changes in fetal body weight and reduced ossification. For maternal rats, the NOEL was 250 mg/kg-day based upon liver weight and behavior. In rabbits, no fetal or embryo-toxicity was noted and there were no treatment-related malformations or developmental variations; thus, the NOEC for offspring was 250 mg/kg-day. Treatment-related maternal effects in rabbits included mortality, spontaneous abortion, behavioral effects, and reduced feed consumption and body weight. The NOEL for maternal effects in rabbits was 25 mg/kg-day.

Zirconium tetrachloride (or other salts)
There are no developmental toxicity studies available for zirconium tetrachloride or other zirconium salts.

Reproduction Studies

Hexanoic acid, 2-ethyl, zirconium salt
There are no reproduction studies available for hexanoic acid, 2-ethyl, zirconium salt.

2-ethylhexanoic acid

A one-generation reproduction study was conducted with 2-ethylhexanoic acid (as sodium 2-ethylhexanoate). Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating and during cohabitation; pregnant females were treated during gestation and lactation. The NOEL was reported as 300 mg/kg for the parental generation and as 100 mg/kg for the F1 generation.

Zirconium tetrachloride (or other salts)

There are no studies on developmental toxicity of zirconium tetrachloride or other zirconium salts.

Other Information

Zirconium

Long term exposure to zirconium may enhance the humoral immune response and induce a state of hypersensitivity, based upon an enhanced response of immunoglobin-M (IgM) antibody production in mice that have been intraperitoneally injected with zirconium oxychloride at low doses. Zirconium sulfate administered at 5 ppm in drinking water in lifetime studies with rats (where the diet contained an additional 2.6 ppm) indicated no evidence of any biological or toxicological activity of zirconium, except to inconsistently affect the body weight of older animals. There was no evidence that zirconium was tumorigenic in a rat strain (Long-Evans) with appreciable (20%) tumor incidence

Table 2. Summary of existing data for hexanoic acid, 2-ethyl, zirconium salt and its dissociation products[1]

SIDS ENDPOINT	REPORTED VALUES		
	Hexanoic acid, 2-ethyl, zirconium salt	**2-ethylhexanoic acid**	**Zirconium tetrachloride[2]**
Physicochemical Properties			
Melting Point	<-75°C	-118.4ºC	437ºC
Boiling Point	204.5 – 206.8ºC	227.6ºC	--
Density	--	--	2.803 at 15ºC
Vapor pressure	NR[4]	1.33×10^{-3} kPa at 20ºC	1 mm Hg at 190ºC
Log Partition Coefficient	4.37	3.0	NR
Water Solubility	0.5 µg/L at 20ºC	25 mg/L at 25ºC	Soluble in cold water
Environmental Fate			
Photodegradation	--	Half-life of 16 hours for indirect photolysis	NR
Dissociation in water	pKa = 5.81, 7.09, 7.65, and 8.24 at 20ºC	--	--
Monitoring Data	--	--	--
Transport (Fugacity)	NR	5.29% in air, 41.6% in water, 53% in soil, 0.197% in sediment	NR
Biodegradation	--	BOD_{20} at 83% of theoretical	NR
Ecotoxicity			
Fish toxicity (96-h LC50)	Reliable data not available	70 mg/L (fathead minnow)	> 20 mg Zr/L (rainbow trout); 15 – 270 mg Zr/L for $ZrOCl_2$ (bluegill, fathead minnow)
Invertebrate toxicity (48-h EC50)	Reliable data not available	85.4 mg/L (*Daphnia magna*)	Reliable data not available
Algae toxicity (96-h EC50)	Reliable data not available	40.6 – 44.4 mg/L (*Scenedesmus subspicatus*)	2.6 mg Zr/L (*Selenastrum capricornutum*)

SIDS ENDPOINT	REPORTED VALUES		
	Hexanoic acid, 2-ethyl, zirconium salt	**2-ethylhexanoic acid**	**Zirconium tetrachloride[2]**
Human Health Effects			
Acute Oral LD50	> 5000 mg/kg (rat)	1600 – 3200 mg/kg (rat)	438 mg/kg (mouse); 700 mg/kg (rat). For $ZrOCl_2$, 1227 mg/kg (mouse); 3500 mg/kg (rat)
Inhalation LC50	> 8.8 mg/L (rat; 1 hr exposure)	> 2.36 mg/L (rat; 6 hr exposure)	Effects observed from inhalation of 6 mg Zr/m^3 for 60 days
Dermal LD50	> 5000 mg/kg (rabbit)	< 5.0 mL/kg (guinea pig)	--
Skin irritation	Not a primary skin irritant to rabbits; primary skin irritant and fatiguing agent to guinea pigs	Slight necrosis in rabbits after 4 hrs.	No sensitization in guinea pigs or mice
Eye irritation	Not a primary eye irritant (rabbit)	Severe corneal irritation in rabbits after 24 hours	Zirconium compounds are eye irritants
Repeated dose	--	For 13-week dietary exposure, NOAEL ~300 mg/kg-day for rats and ~200 mg/kg-day for mice	230 mg Zr/kg (as $ZrOCl_2$) did not affect survival, behavior or growth of rats dosed via gastric tube for 16 days; no effect of 5 ppm $ZrSO_4$ in rats via drinking water over lifetime
Genetic toxicity *(in vitro)*	Negative in Ames assay with *Salmonella*; negative in bacterial DNA damage/repair assay with *E. coli*	Negative in Ames assay with *Salmonella*	Negative in His^+ reverse fluctuation assay with *Salmonella*; negative in SOS Chromotest with *E. coli.*
Genetic toxicity *(in vivo)*	Negative in mouse micronucleus test	Negative in mouse micronucleus test	Chromosomal abnormalities in mouse bone marrow and human leucocytes ($ZrOCl_2$)

SIDS ENDPOINT	REPORTED VALUES		
	Hexanoic acid, 2-ethyl, zirconium salt	**2-ethylhexanoic acid**	**Zirconium tetrachloride[2]**
Developmental	--	No evidence of teratogenicity. In rats, NOEL = 100 mg/kg/day for offspring, 250 mg/kg-day for maternal animals. For rabbits, NOEL = 250 mg/kg for offspring, 25 mg/kg for maternal animals	--
Reproductive	--	NOEL = 300 mg/kg for parental generation, 100 mg/kg for F1 generation (rats)	--

[1] References are given in the robust summaries (Appendixes A – C)
[2] Data are for zirconium tetrachloride, except as specifically noted
[3] Zirconium versalate is a mixture of hexanoic acid, 2-ethyl, zirconium salt (75-85% by weight) and mineral spirits
[4] NR = not relevant

TEST PLAN AND RATIONALE FOR HEXANOIC ACID, 2-ETHYL, ZIRCONIUM SALT

Hexanoic acid, 2-ethyl, zirconium salt	CASRN 22464-99-9

The Test Plan for Hexanoic acid, 2-ethyl, zirconium salt, is presented in Table 3 with supporting data for the dissociation products. The rationale for the Test Plan is based upon existing data as summarized in the previous section and in Table 2.

Physicochemical Properties

With the exception of density, data are available for all five SIDS endpoints listed in Tables 2 and 3 for either the hexanoic acid, 2-ethyl, zirconium salt or 2-ethylhexanoic acid, if not both. GLP studies were conducted to determine melting point, boiling point, and water solubility of hexanoic acid, 2-ethyl, zirconium salt. The vapor pressure endpoint is considered not applicable for the salt, and the octanol/water partition coefficient was estimated using WSKOW v.1.41.

- No additional testing is recommended or proposed for any of the physico-chemical properties.

Environmental Fate Parameters

A GLP study was conducted to determine the dissociation constant for hexanoic acid, 2-ethyl, zirconium salt. This is a key property, because the fate and effects of the compound are based upon the dissociation products. Of these dissociation products, environmental fate endpoints such as photodegradation, fugacity, or biodegradation are not relevant for zirconium tetrachloride because zirconium is an element which does not degrade further. For 2-ethylhexanoic acid, experimental data are available for the biodegradation endpoint, which indicates that this material is biodegradable. The values for the photodegradation and fugacity endpoints for 2-ethylhexanoic acid were predicted using EPIWIN (Appendix A). Standard models used for estimating fugacity (transport) do not accurately predict salts or ionized substances and were not used for hexanoic acid, 2-ethyl, zirconium salt.

- Testing is recommended to determine the biodegradation of hexanoic acid, 2-ethyl, zirconium salt.

Ecotoxicity

No reliable ecotoxicity studies are available for hexanoic acid, 2-ethyl, zirconium salt. Sufficient data are available for both dissociation products for fish and algae. In addition, data on invertebrate toxicity are available for 2-ethylhexanoic acid. Reliable data on invertebrate toxicity are lacking for zirconium tetrachloride. Since the available ecotoxicity data indicates that the zirconium moiety is more toxic to aquatic organisms than 2-ethylhexanoic acid, the invertebrate data for 2-ethylhexanoic acid is insufficient to assess the toxicity of hexanoic acid, 2-ethyl, zirconium salt. Therefore, an acute toxicity test with *Daphnia* is recommended for hexanoic acid, 2-ethyl, zirconium salt.

- An acute toxicity test with daphnids is proposed for hexanoic acid, 2-ethyl, zirconium salt.

Human Health Effects

Acute toxicity studies

Acute toxicity data are available for hexanoic acid, 2-ethyl, zirconium salt for all five endpoints (oral toxicity, inhalation, dermal toxicity, skin irritation, and eye irritation). Data are also available for essentially all of these endpoints for the dissociation products.

- No additional acute mammalian toxicity testing is recommended or proposed for hexanoic acid, 2-ethyl, zirconium salt.

Genotoxicity studies

Both *in vitro* and *in vivo* genotoxicity studies have been conducted on hexanoic acid, 2-ethyl, zirconium salt, with consistent results indicative of no mutagenic activity.

No additional genotoxicity studies are recommended or proposed for hexanoic acid, 2-ethyl, zirconium salt.

Higher tiered studies

Several repeated dose studies have been conducted with 2-ethylhexanoic acid. Repeated dose studies have also been conducted with zirconium compounds (zirconium oxychloride and zirconium sulfate). There are no repeat dose data available for hexanoic acid, 2-ethyl, zirconium salt. The developmental and reproductive toxicity of 2-ethylhexanoic acid has been studied in rats and rabbits.

No developmental or reproductive data are available for hexanoic acid, 2-ethyl, zirconium salt or for zirconium tetrachloride.

- A combined repeated dose with repro/developmental screen (OECD 422) is proposed for hexanoic acid, 2-ethyl, zirconium salt.

Table 3. Test Plan Matrix: Hexanoic acid, 2-ethyl, zirconium salt

Data Elements	Hexanoic acid, 2-ethyl, zirconium salt			2-ethyl-hexanoic acid			Zirconium tetrachloride			Testing recommended for Hexanoic acid, 2-ethyl, zirconium salt
	Information available	GLP study	Acceptable	Information available	GLP study	Acceptable	Information available	GLP study	Acceptable	
Melting Point	N	Y	Y	Y	N	Y	Y	N	Y	N
Boiling Point	Y	Y	Y	Y	N	Y	N			N
Vapor pressure	--			Y	N	Y	Y	N	Y	N
Partition Coefficient	Y	N	Y	Y	N	Y	--			N
Water Solubility	Y	Y	Y	Y	N	Y	Y	N	Y	N
Photodegradation	N			Y	N	Y	--			N
Dissociation in water	Y	Y	Y	N			N			N
Transport (Fugacity)	--			Y	N	Y	--			N
Biodegradation	N			Y	N	Y	--			Y
Fish toxicity (96-h)	Y	N	N	Y	N	Y	Y	N	Y	N
Invertebrate toxicity (48-h)	Y	N	N	Y	N	Y	Y	N	N	Y
Algae toxicity (72-h)	Y	N	N	Y	N	Y	Y	N	Y	N
Acute										
Oral LD50	Y	N	Y	Y	N	Y	Y	N	Y	N
Inhalation LC50	Y	N	Y	Y	N	N	Y	N	N	N
Dermal LD50	Y	N	Y	Y	N	N	N			N
Skin Irritation	Y	N	Y	Y	Y	Y	Y	N	N	N
Eye Irritation	Y	N	Y	Y	N	N	Y	N	N	N
Repeated dose	N			Y	Y	Y	Y	N	N	Y[b]
Genetic Toxicology – mutation assay	Y	N	Y	Y	N	Y	Y	N	Y	N
Genetic Toxicology – *in vivo*	Y	Y	Y	Y	Y	Y	Y	N	Y	N
Reproductive	N			Y	N	N	N			Y[b]
Developmental	N			Y	Y	Y	N			Y[b]

b = OECD 422 proposed
-- means not relevant

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APPENDIX A:

ROBUST SUMMARIES FOR HEXANOIC ACID, 2-ETHYL, ZIRCONIUM SALT

APPENDIX B:

ROBUST SUMMARIES FOR 2-ETHYLHEXANOIC ACID

APPENDIX C:

ROBUST SUMMARIES FOR ZIRCONIUM TETRACHLORIDE